AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD1656
Study Code	D1020C00031
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An Open-label, Randomised, Placebo-Controlled, Two-Way Crossover, Phase I Single Centre Study in Type 2 Diabetes Mellitus Patients Treated with Metformin to Evaluate the Pharmacokinetics of Digoxin During Co-Administration with AZD1656

Study dates: First patient enrolled: 13 September 2010
Last patient last visit: 14 December 2010

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre

The study was conducted at 1 study centre in the United States (Profil Institute for Clinical Research Inc., California).

Publications

None at the time of writing this clinical study report (CSR).

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
Evaluate the pharmacokinetics (PK) of digoxin after a single dose when administered alone and in combination with AZD1656 at steady state	AUC and C_{max}	PK
Secondary	**Secondary**	
Evaluate the safety of AZD1656 in combination with digoxin	Electrocardiogram (ECG), weight, pulse rate, blood pressure, safety laboratory variables (including 7-point glucose), physical examination, and adverse events (AEs)	Safety
Describe the PK of AZD1656 and its metabolite AZD5658 during concomitant digoxin administration	$AUC_{(0-24)}$, C_{max}, C_{trough}, t_{max}, $t_{1/2}$, and CL/F (AZD1656 only)	PK
Describe the PK of digoxin when administered alone or in combination with AZD1656	t_{max} and $t_{1/2}$	PK
Exploratory		
Explore postprandial glucose-insulin response	$AUC_{(0-4)}$ for both insulin and glucose	Pharmacodynamics (PD)
Collect and store DNA samples for potential future research into genes which may influence response (PK profile, drug disposition, efficacy, safety, and tolerability) to AZD1656, metformin, and digoxin	Not applicable	Pharmacogenetic

AUC Area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0-4)}$ Postprandial area under the observed plasma concentration-time curve from time zero to 4 hours.
$AUC_{(0-24)}$ Area under the plasma concentration-time curve from time zero to 24 hours
C_{max} Maximum plasma concentration. For AZD1656 and its metabolite AZD5658 the parameter was calculated for the morning (AM) dose
CL/F Oral clearance, calculated as total daily dose/$AUC_{(0-24)}$ (ie, (AM+PM dose)/$AUC_{(0-24)}$; determined for AZD1656 only)
C_{trough} Trough concentrations were measured for AZD1656 and its metabolite AZD5658 on Day 4, Day 5, Day 6, Day 7, and Day 8
$t_{1/2}$ Terminal plasma half-life, calculated by $\ln 2/\lambda$
t_{max} Time to maximum concentration
Note: Results from any genetic research, if performed, will be reported separately from this CSR

Study design

This was an open-label, randomised, placebo-controlled, 2-way crossover, single centre, drug-drug interaction Phase I study in patients with Type 2 diabetes mellitus (T2DM). Male and female patients of nonchildbearing potential, aged ≥18 years, treated with metformin only or metformin and one other oral antidiabetic drug (OAD; sulphonylurea [SU] or dipeptidase-4 inhibitor [DPP-4-inhibitor]) were enrolled in the study.

The investigational products were administered in a crossover design in either sequence AB or sequence BA. Treatment A included AZD1656 twice daily from Day 1 to Day 7 and digoxin 0.5 mg on Day 4, and Treatment B included placebo twice daily from Day 1 to Day 7 and digoxin 0.5 mg on Day 4. Eligible patients treated with a SU or a DPP-4-inhibitor, stopped taking their SU or DPP-4-inhibitor 7 days to 10 days (wash-out period) before administration of AZD1656/placebo on Day 1.

On Day 1, patients received AZD1656 40 mg/placebo twice daily, on Day 2, patients received AZD1656 100 mg/placebo twice daily, and on Day 3 to Day 7, patients received AZD1656 100 mg/placebo twice daily or if this was not well tolerated on Day 2, AZD1656 40 mg/placebo twice daily. A single dose of 0.5 mg digoxin was administered in the morning of Day 4 during each treatment period. The treatment periods were separated by a 2-day to 5-day wash-out period.

Blood samples for analysis of plasma concentrations of digoxin, AZD1656 and its metabolite AZD5658 were taken during the 96 hours following the administration of digoxin.

Target subject population and sample size

The target population was males and females of nonchildbearing potential with T2DM aged ≥18 years, with a body mass index (BMI) ≥19 and ≤42 kg/m^2, treated with either metformin alone or metformin and one other OAD (SU or DPP-4-inhibitor). Eligible patients continued their metformin treatment during the study. Twenty patients were randomised in order to have 16 evaluable patients.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

- AZD1656, 40 mg ([as 2 x 20 mg oral tablets] twice daily or 100 mg [as 2 x 50 mg oral tablets] twice daily, manufactured by AstraZeneca,
  Batch number 09-007136AZ and 09-007135AZ, respectively)

- AZD1656 placebo, matching oral tablets twice daily, manufactured by AstraZeneca, Batch number 09-003942AZ

- Digoxin, 0.5 mg oral tablet on Day 4 of each treatment period, manufactured by Global Pharmaceuticals, Batch number 050051

Duration of treatment

There were 2 treatment periods of 7 days each with a 2-day to 5-day wash-out period between the treatment periods.

Statistical methods

Plasma concentrations of AZD1656, the metabolite AZD5658, and digoxin, and the derived PK parameters were summarised by treatment using descriptive statistics.

To assess the effect of AZD1656 on digoxin PK, the PK parameters of digoxin were analysed using an analysis of variance model (ANOVA) on the log-transformed digoxin $AUC_{(0-t)}$ and C_{max} with fixed effects for sequence, period, and treatment and patient nested within sequence as a random effect. Ratios of geometric means for the test (AZD1656 + digoxin treatment group) versus reference (placebo + digoxin treatment group) and the associated 90% confidence intervals (CIs) were presented.

The PD (observed postprandial glucose and insulin) concentrations as well the derived PD parameters were summarised using descriptive statistics.

Adverse events were summarised by incidence within treatment. Safety laboratory measurements, ECGs, and vital signs were summarised by treatment group and time points within treatment groups.

Subject population

A total of 20 patients with T2DM were randomised in this study. The first patient was enrolled on 13 September 2010 and the last patient completed the study on 14 December 2010. Three (3) patients prematurely withdrew from the study. Two (2) of the 3 patients were discontinued from AZD1656 due to an AE. Patient E0001016 was discontinued due to an AE of ECG change and Patient E0001028 was discontinued due to an AE of hypoglycaemia.

Summary of pharmacokinetic results

Digoxin AUC was estimable in only 8 patients (4 patients with AUC in both treatment groups; 2 patients with AUC in the AZD1656 + digoxin treatment group and 2 patients with AUC in the placebo + digoxin treatment group) and hence $AUC_{(0-t)}$, which was estimable in all patients, was included in the statistical analyses. The geometric least squares (LS) mean ratio (AZD1656 + digoxin treatment group and placebo + digoxin treatment group) for $AUC_{(0-t)}$ of digoxin was 102.49% (90% CI: 90.86%, 115.62%). The 90% CI for the ratio of $AUC_{(0-t)}$ was contained entirely within the interval of 80.00% to 125.00%.

The geometric LS mean ratio (AZD1656 + digoxin treatment group and placebo + digoxin treatment group) for C_{max} of digoxin was 122.70% (90% CI: 100.30%, 150.11%). The 90% CI for the geometric mean ratio of C_{max} was not entirely contained within the interval of 80.00% to 125.00%.

Following 4 days of multiple-dose administration (AZD1656 100 mg twice daily) in patients with T2DM in the presence of digoxin, AZD1656 had a geometric mean C_{max} of 4.28 µmol/L, and $AUC_{(0-24)}$ of 46.0 µmol*h/L with an elimination half-life of 4.59 hours and a CL/F of 9.08 L/h; whereas AZD5658 had a C_{max} of 0.456 µmol/L and an $AUC_{(0-24)}$ of 6.44 µmol*h/L. Based on visual inspection of data, steady state concentrations were reached by Day 4 for both AZD1656 and AZD5658.

The PK parameters t_{max}, $t_{1/2}$, and CL/F for digoxin appear to be similar between the 2 treatments (AZD1656 + digoxin treatment group and placebo + digoxin treatment group).

Summary of pharmacodynamic results

Overall mean levels of postprandial insulin were lower on Day 4 both with digoxin alone and digoxin in combination with AZD1656 as compared to Day 1.

Overall mean postprandial glucose levels were lower on Day 4 as compared to Day 1 when AZD1656 was administered in combination with digoxin. Mean plasma glucose levels in the AZD1656 + digoxin treatment group were lower on Day 1 and Day 4 when compared to placebo + digoxin treatment group.

The postprandial $AUC_{(0-4)}$ of insulin and glucose were comparable between Day 4 and Day 1 for the placebo + digoxin treatment group. The postprandial $AUC_{(0-4)}$ of insulin and glucose were lower on Day 4 in comparison to Day 1 for the AZD1656 + digoxin treatment group.

Summary of safety results

No deaths, serious adverse events (SAEs), or other significant AEs (OAEs) were reported in the study, whilst 2 patients were discontinued from AZD1656 due to AEs. Patient E0001016 was discontinued due to an AE of ECG change after receiving AZD1656 from Day 1 to Day 3, before receiving digoxin on Day 4, and Patient E0001028 was discontinued due to an AE of hypoglycaemia after receiving AZD1656 from Day 1 to Day 6, after receiving digoxin on Day 4.

Hypoglycaemic events were only reported by patients in the AZD1656 + digoxin treatment group. In all hypoglycaemic events the plasma glucose levels were ≥3.0 mmol/L. These plasma glucose data are in line with previous hypoglycaemic events observed in patients with T2DM following multiple dose administration of AZD1656.

There were no clinically relevant changes in clinical laboratory, vital signs, ECG, physical examination findings, or weight.